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(54) Title: TOPICAL TREATMENT OF OCULAR PHOTOPHOBIA

(57) Abstract

The use of a non-steroidal antiinflammatory agent in the preparation of an ophthalmic pharmaceutical composition for the prevention, treatment or control of ocular photophobia is described.

FOR THE PURPOSES OF INFORMATION ONLY

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TOPICAL TREATMENT OF OCULAR PHOTOPHOBIA

This invention relates to the use of a non-steroidal antiinflammatory agent in a therapeutically effective amount in the preparation of an ophthalmic pharmaceutical composition in combination with an ophthalmically acceptable carrier for treating or preventing ocular photophobia of a mammal; to a method for the topical prevention, control and treatment of ocular photophobia resulting from a variety of ocular conditions, ocular examinations and ocular surgery; and particularly to the topical ophthalmic use of a nonsteroidal anti-inflammatory agent for the treatment of ocular photophobia in mammals.

Photophobia is an abnormal visual intolerance to light, in particular to strong light. Ocular photophobia as used herein denotes photophobia of ocular origin, such as photophobia associated with various ocular disorders, ocular examination procedures or ocular surgery.

Ocular disorders resulting in ocular photophobia comprise allergic conditions such as acute seasonal allergic conjunctivitis, keratoconjunctivitis, keratitis sicca, keratouveitis, chronic non-infectious conjunctivitis, infectious conjunctivitis, uveitis, iridocyclitis, iritis, and disruptions to the blood-aqueous-barrier.

Ocular examination procedures resulting in ocular photophobia involve ocular examinations by various ophthalmological techniques, such as dilated eye exams.

Surgical procedures resulting in ocular photophobia comprise extracapsular cataract extraction, phacoemulsification cataract extraction, laser capsulotomy, epikeratophakia, penetrating keratoplasty, lamellar keratoplasty, automated lamellar keratoplasty, incisional keratotomy, radial keratotomy, astigmatic keratotomy, photorefractive keratectomy, phototherapeutic keratectomy, conjunctival flaps, pterygium excision, prosthokeratoplasty, trabeculectomy, laser trabeculoplasty, laser iridectomy, and cyclodestructive procedures. The photorefractive keratectomy or phototherapeutic keratectomy is performed with one or more frequencies of laser energy involving excimer and/or intrastromal lasers.

Systemic administration of certain non-steroidal antiinflammatory agents has been reported to influence ocular sensitivity to light (photophobia).

Photophobia has been reported as a potential side effect for systemically administered benoxaprofen (British Med. J. 284, 1784, June 12, 1982). On the other hand photophobia associated with migraine headache is reduced with ketorolac administered intramuscularly (Ann. Emerg. Med. 21/8, 919-924, 1992); similarly for diclofenac sodium administered orally (J. Int. Med. Res. (UK) 15/1, 44-48, 1987).

The present invention relates to the use of a non-steroidal antiinflammatory agent in the preparation of an ophthalmic pharmaceutical composition for treating or preventing ocular photophobia of a mammal.

The present invention provides a method for the prevention, treatment or control of ocular photophobia associated with diseases and disorders of the eye. The present invention also provides a safe and effective method for the prevention, treatment or control of ocular photophobia associated with ocular surgical procedures and with ocular examinations.

Ocular photophobia as used herein refers to photophobia of ocular origin, that is photophobia due to photophobia-inducing ocular disorders or diseases or due to photophobia-inducing ocular surgical, traumatic and examination procedures.

Photophobia-inducing ocular disorders as used herein refer to allergic conditions such as acute seasonal allergic conjunctivitis, keratoconjunctivitis, keratitis sicca, keratouveitis, chronic non-infectious conjunctivitis, infectious conjunctivitis, uveitis, iridocyclitis, iritis and to disruptions to the blood-aqueous-barrier. Ocular photophobia as used herein refers preferably to allergic conditions such as acute seasonal allergic conjunctivitis, keratoconjunctivitis, keratitis sicca, keratouveitis, chronic non-infectious conjunctivitis and infectious conjunctivitis, and more preferably to acute seasonal allergic conjunctivitis.

These and other objects are accomplished in accordance with the present invention which provides a method of treating or controlling ocular photophobia which comprises administering topically to the affected eye of a mammal, including a human host, a therapeutically effective amount of an ophthalmic composition of a nonsteroidal ocularly suitable anti-inflammatory drug in a pharmaceutical acceptable carrier.

The present method can be safely used to substantially reduce the ocular photophobia resulting from various causes as discussed hereinabove. Thus, the method of the present invention would eliminate a significant ocular problem and offers readily apparent

advantages over the inconveniences afforded by conventional methods of alleviating the discomfort of photophobia, i.e., sunglasses or eye bandages.

The foregoing and other aspects, advantages and objects of the invention may be more fully appreciated by reference to the following detailed description.

More particularly, the present invention relates to the use of a non-steroidal antiinflammatory agent in a therapeutically effective amount in the preparation of an ophthalmic pharmaceutical composition in combination with an ophthalmically acceptable carrier for treating or preventing ocular photophobia of a mammal.

The present invention relates to a method of treating ocular photophobia in mammals which comprises administering topically to the eye of a mammal in need thereof a therapeutically effective amount of an ophthalmic composition of an ocularly suitable non-steroidal antiinflammatory drug in combination with an ocularly acceptable carrier.

Suitable non-steroidal antiinflammatory agents are those well-known in the art, including fenamates, oxicams, arylacetic acids, arylpropionic acids and the like, preferably indomethacin, sulindac, diclofenac, suprofen, oxaprozin, naproxen, flurbiprofen, etodolac, ketorolac, ketoprofen, meclofenamic acid, tenidap, piroxicam, tolmetin, and ophthalmically acceptable salts thereof. Preferred salts are alkali metal salts, such as the sodium or potassium salt, and ammonium salts, such as the tromethamine and diethylammonium salts.

Preferred non-steroidal antiinflammatory agents are indomethacin, diclofenac, piroxicam, flurbiprofen, suprofen, ketorolac and ophthalmically acceptable salts thereof. More preferred non-steroidal antiinflammatory agents are indomethacin, diclofenac, piroxicam, flurbiprofen and ophthalmically acceptable salts thereof. Highly preferred is diclofenac and ophthalmically acceptable salts thereof. Strongly preferred is diclofenac sodium.

Such non-steroidal antiinflammatory agents can be administered as solutions, gels, suspensions, dispersions, ointments or creams using suitable ophthalmic carriers well-known to those skilled in the art.

Concentration of active ingredient ranges from about 0.001% to about 5%, preferably about 0.01% to about 2%, depending on the compound and formulation involved.

The non-steroidal antiinflammatory agent is preferably administered in the form of a sterile aqueous solution or suspension, preferably hypotonic or isotonic, and having a pH ranging from about 4.0 to 9.7, preferably from about 4.5 to 7.5 and more preferably from 6.0 to 7.5.

The formulations are prepared using carriers well-known in the art. For example, suitable formulations of diclofenac and salts thereof are described in U.S. patents 4,960,799 and 4,829,088, which are incorporated herein by reference.

Examples of suitable carriers are especially water, mixtures of water and water-miscible solvents, such as C_1- to C_7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5 % by weight hydroxyethylcellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone and other non-toxic water-soluble polymers for ophthalmic uses, such as, for example, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, acrylates or methacrylates, such as salts of polyacrylic acid or ethyl acrylate, polyacrylamides, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, such as neutral Carbopol, or mixtures of those polymers. Preferred carriers are water, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, neutral Carbopol, or mixtures thereof. The concentration of the carrier is, for example, from 1 to 100 000 times the concentration of the active ingredient.

Examples of commercial ophthalmic preparations suitable in the instant invention are diclofenac sodium 0.1% sterile ophthalmic solution (Voltaren Ophthalmic, Ciba-Vision Ophthalmics, U.S.A.), flurbiprofen sodium 0.03% sterile ophthalmic solution (Ocufen, Allergan Medical Optics, U.S.A.), suprofen 1% sterile ophthalmic solution (Profenal, Alcon Surgical, Inc., U.S.A.) and ketorolac tromethamine 0.5% sterile ophthalmic solution (Acular, Allergan, Inc., U.S.A.).

Typically, one drop (about 25-50 µl) of the ophthalmic solution is administered to the eye

of a patient in need thereof about two to eight times a day. For surgical procedures, the ophthalmic solution is administered 30 to 60 minutes before surgery, and again right after surgery and administration is continued as required.

The photophobia of patients exposed to ambient room light, a penlight, daylight or other source of light stimulation is rated as none, mild, moderate or severe in order to determine the elimination or reduction of photophobia on treatment with the non-steroidal antiinflammatory agent in comparison to patients administered placebo vehicle only.

The use of topically administered non-steroidal antiinflammatory agents to significantly reduce photophobia associated with ocular disorders, ocular examinations, ocular trauma (e.g. corneal abrasions, removal of foreign bodies), retinal detachment surgery and ocular surgery represents an innovative medicinal approach to treating and/or controlling ocular photophobia which has been treated until now only by prescribing the use of eyeglasses, preferably sunglasses.

The following examples are presented for illustrative purposes and are not intended to limit the scope of the invention.

The diclofenac sodium 0.1% ophthalmic solution (DSOS) used in the following studies is prepared substantially according to U.S. patent 4,960,799.

The formulation is as follows:

Material	Amount Per ml
Diclofenac Sodium	1.00 mg
Tromethamine, U.S.P.	9.36 mg
Sorbic Acid, N.F.	2.00 mg
Boric Acid, N.F.	14.25 mg
Edetate Disodium, U.S.P.	1.00 mg
Polyoxyl 35 Castor Oil, N.F.	50.00 mg
Purified Water, U.S.P.	qs 1 ml

The placebo vehicle ophthalmic solution (PVOS) used in the following studies is:

Material	Amount Per ml
Tromethamine, U.S.P.	9.36 mg
Sorbic Acid, N.F.	2.00 mg
Boric Acid, N.F.	14.25 mg
Edetate Disodium, U.S.P.	1.00 mg
Polyoxyl 35 Castor Oil, N.F.	50.00 mg
Purified Water, U.S.P.	qs 1 ml

Examples

Clinical Study 1: A prospective, randomized, double-masked, parallel group comparison study of diclofenac sodium 0.1% ophthalmic solution (DSOS) with its placebo vehicle ophthalmic solution (PVOS) is performed. Patients with clinically documented acute seasonal allergic conjunctivitis are enrolled for clinical evaluation. The study procedures involve one drop of DSOS or PVOS immediately following the enrollment examination and then every two hours for a maximum of eight doses daily for two days and then every four to six hours for a maximum of four doses daily for the next twelve days. Twenty patients (DSOS=10; PVOS=10) are evaluated at 30 minutes following the first dose and then after two, seven and fourteen days of masked treatment. Patients in both treatment groups display photophobia of varying severity when enrolled into the study. On average, patients that received PVOS experienced little change in their photophobia severity score while patients that received DSOS experienced significant improvement. In DSOS treated patients, improvement in the mean photophobia score from baseline is observed as early as 30 minutes after the first dose is administered to the eye and continued throughout the fourteen days of treatment.

Clinical Study 2: A prospective, randomized, double-masked, fellow-eye comparison study of diclofenac sodium 0.1% ophthalmic solution (DSOS) with its placebo vehicle ophthalmic solution (PVOS) is performed. Patients with bilateral myopia that are scheduled for bilateral radial keratotomy surgery are enrolled for clinical evaluation. The study procedures involve one drop of DSOS or PVOS 30 to 60 minutes before surgery, one drop after surgery, and one drop six hours after surgery into the specified eyes. Twenty-one patients (DSOS=21 eyes; PVOS=21 eyes) are evaluated prior to the first dose, at 0.5, 1, 1.5, 2, 4 and 6 hours after surgery, and again at either 24 or 48 hours after

surgery. Both eyes of all patients are without photophobia symptoms prior to surgery and then experienced a significant postsurgical photophobia that peaks by one hour after surgery. On average, eyes that received PVOS experience little change in their photophobia severity score over the next 24 to 48 hours while eyes that receive DSOS experience significant improvement for up to 24 hours after surgery. In the DSOS treated eyes, the improvement in photophobia is observed as early as 1.5 hours after surgery and continues through at least 24 hours postsurgically.

Clinical Study 3: A prospective, randomized, double-masked, parallel-group comparison study of diclofenac sodium 0.1% ophthalmic solution (DSOS) with its placebo vehicle ophthalmic solution (PVOS) is performed. Patients with myopia that are scheduled for unilateral radial keratotomy surgery are enrolled for clinical evaluation. The study procedures involve one drop of DSOS or PVOS 30 to 60 minutes before surgery, one drop after surgery, and one drop six hours after surgery into the specified eyes. Forty-five patients (DSOS=24; PVOS=21) are evaluated prior to the first dose, at 0.5, 1, 1.5, 2, 4 and 6 hours after surgery, and again at 24 hours after surgery. Patients in both treatment groups are without photophobia symptoms prior to surgery and then experience a significant postsurgical photophobia that peaks by two hours after surgery. On average, eyes that receive PVOS experience little change in their photophobia severity score over the next 24 hours while eyes that receive DSOS experience significant improvement for up to 24 hours after surgery. In the DSOS treated eyes, the improvement in photophobia is observed as early as 4 hours after surgery and continues through at least 24 hours postsurgically.

Clinical Study 4: A prospective, randomized, double-masked, parallel-group comparison study of diclofenac sodium 0.1% ophthalmic solution (DSOS) with its placebo vehicle ophthalmic solution (PVOS) is performed. Patients with myopia that are scheduled for unilateral excimer laser photorefractive keratectomy surgery are enrolled for clinical evaluation. The study procedures involve two drops given 5 minutes apart of DSOS or PVOS after surgery and then one drop every six hours to allow for four daily doses in the surgically-treated eye until the cornea is completely reepithelialized. Thirty-two patients (DSOS=16; PVOS=16) are evaluated prior to the first dose, at 0.5, 1, 1.5, 2, 4, 12, 18 and 24 hours after surgery. Daily followup examinations are scheduled until corneal reepithelialization is complete. Patients in both treatment groups are without photophobia symptoms prior to surgery and then experience a significant postsurgical photophobia that peaks by two to four hours after surgery. On average, eyes that receive PVOS experience

little change in their photophobia severity score over the next 48 hours while eyes that receive DSOS experience significant improvement for up to 48 hours after surgery. In the DSOS treated eyes, the improvement in photophobia is observed as early as 4 hours after surgery and continues through at least 48 hours postsurgically.

Clinical Study 5: A prospective, randomized, double-masked, parallel-group comparison study of diclofenac sodium 0.1% ophthalmic solution (DSOS) with its placebo vehicle ophthalmic solution (PVOS) is performed. Twenty normal or patient volunteers (40 healthy eyes) undergoing bilateral pupil dilatation for routine fundus examination are enrolled for clinical evaluation. All eyes have pupil dilatation using 1 drop of tropicamide (1.0 %) and 1 drop of phenylephrine (2.5 %). In addition 1 eye of each patient received 2 drops of the PVOS in a random order 5 minutes after the instillation of the above dilating drops. Light sensitivity and pupil size are measured 30, 60, 90 and 120 minutes after instillation of the dilating drops. Photophobia is assessed by the patient on a verbal rating scale (VRS) and visual analogue scale (VAS). For a more objective assessment neutral density filters of increasing strengths are placed in front of the eye until the photosensitivity on the VAS scale is reduced to zero. A statistically significant difference is noticed over the entire observation period in favor of DSOS as compared to PVOS.

CLAIMS

1. The use of a non-steroidal antiinflammatory agent in a therapeutically effective amount in the preparation of an ophthalmic pharmaceutical composition in combination with an ophthalmically acceptable carrier for treating or preventing ocular photophobia of a mammal.

2. The use according to claim 1 wherein the antiinflammatory agent is selected from the group consisting of a fenamate, an oxicam, an arylacetic acid and an arylpropionic acid, and ophthalmically acceptable salts thereof.

3. The use according to claim 1 wherein the antiinflammatory agent is selected from the group consisting of indomethacin, sulindac, diclofenac, suprofen, oxaprozin, naproxen, flurbiprofen, etodolac, ketorolac, ketoprofen, meclofenamic acid, piroxicam, tenidap and tolmetin, and ophthalmically acceptable salts thereof.

4. The use according to claim 1 wherein the pharmaceutical composition is a sterile solution or suspension having a pH ranging from about 4.0 to 9.7, preferably from about 4.5 to 7.5 and more preferably from 6.0 to 7.5.

5. The use of a non-steroidal antiinflammatory drug selected from the group consisting of diclofenac, piroxicam, flurbiprofen, suprofen, ketorolac, indomethacin and ophthalmically acceptable salts thereof, in the preparation of an aqueous ophthalmic solution or suspension comprising a therapeutically effective amount of said non-steroidal antiinflammatory drug and an ophthalmically acceptable carrier, for preventing or treating ocular photophobia of a human host.

6. The use according to claim 5 wherein said non-steroidal antiinflammatory agent is diclofenac or an ophthalmically acceptable salt thereof.

7. The use according to claim 5 wherein the non-steroidal antiinflammatory agent is diclofenac sodium.

8. The use according to claim 1 for treating ocular photophobia resulting from acute seasonal allergic conjunctivitis, keratoconjunctivitis, keratitis sicca, keratouveitis, chronic non-infectious conjunctivitis, infectious conjunctivitis, uveitis, iridocyclitis, iritis,

disruptions to the blood-aqueous-barrier, ocular trauma, retinal detachment surgery and dilated ocular examination.

9. The use according to claim 1 for treating ocular photophobia resulting from ocular surgery.

10. The use according to claim 9 wherein said ocular surgery is selected from the group including extracapsular cataract extraction, phacoemulsification cataract extraction, laser capsulotomy, epikeratophakia, penetrating keratoplasty, lamellar keratoplasty, automated lamellar keratoplasty, incisional keratotomy, radial keratotomy, astigmatic keratotomy, conjunctival flaps, pterygium excision, prosthokeratoplasty, trabeculectomy, laser trabeculoplasty, laser iridectomy and cyclodestructive procedures.

11. The use according to claim 9 wherein said ocular surgery is selected from the group of photorefractive keratectomy and phototherapeutic keratectomy.

12. The use according to claim 11 wherein said photorefractive keratectomy or phototherapeutic keratectomy is performed with one or more frequencies of laser energy involving excimer and/or intrastromal lasers.

13. A method of treating or preventing ocular photophobia which comprises administering topically to the eye of a mammal in need thereof a therapeutically effective amount of an ophthalmic pharmaceutical composition of a non-steroidal antiinflammatory agent in combination with an ophthalmically acceptable carrier.

14. The method of claim 13 wherein the antiinflammatory agent is selected from the group consisting of a fenamate, an oxicam, an arylacetic acid and an arylpropionic acid, and ophthalmically acceptable salts thereof.

15. The method according to claim 13 wherein the antiinflammatory agent is selected from the group consisting of indomethacin, sulindac, diclofenac, suprofen, oxaprozin, naproxen, flurbiprofen, etodolac, ketorolac, ketoprofen, meclofenamic acid, piroxicam, tenidap and tolmetin, and ophthalmically acceptable salts thereof.

16. The method according to claim 13 wherein the pharmaceutical composition is a sterile solution or suspension having a pH of about 6.0 to 7.5.

17. The method according to claim 13 of preventing or treating ocular photophobia which comprises administering topically to the eye of a human host in need thereof a therapeutically effective amount of an aqueous ophthalmic solution or suspension of a nonsteroidal antiinflammatory drug selected from the group consisting of diclofenac, piroxicam, flurbiprofen, suprofen, ketorolac, indomethacin, and ophthalmically acceptable salts thereof in an ophthalmically acceptable carrier.

18. The method according to claim 17 wherein said non-steroidal antiinflammatory agent is diclofenac or an ophthalmically acceptable salt thereof.

19. The method according to claim 17 wherein the non-steroidal antiinflammatory agent is diclofenac sodium.

20. The method according to claim 13 of treating ocular photophobia resulting from acute seasonal allergic conjunctivitis, keratoconjunctivitis, keratitis sicca, keratouveitis, chronic non-infectious conjunctivitis, infectious conjunctivitis, uveitis, iridocyclitis, iritis, disruptions to the blood-aqueous-barrier, retinal detachment surgery and dilated ocular examination.

21. The method according to claim 13 of treating ocular photophobia resulting from ocular surgery.

22. The method according to claim 21 wherein said ocular surgery is selected from the group including extracapsular cataract extraction, phacoemulsification cataract extraction, laser capsulotomy, epikeratophakia, penetrating keratoplasty, lamellar keratoplasty, automated lamellar keratoplasty, incisional keratotomy, radial keratotomy, astigmatic keratotomy, conjunctival flaps, pterygium excision, prosthokeratoplasty, trabeculectomy, laser trabeculoplasty, laser iridectomy, and cyclodestructive procedures.

23. The method according to claim 21 wherein said ocular surgery is selected from the group of photorefractive keratectomy and phototherapeutic keratectomy.

24. The method according to claim 23 wherein said photorefractive keratectomy or phototherapeutic keratectomy is performed with one or more frequencies of laser energy involving excimer and/or intrastromal lasers.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/405 A61K31/19 A61K31/38 A61K31/42 A61K31/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REFRACT.CORNEAL.SURG., vol.9, no.6, November 1993 pages 425 - 436 N.A.SHER ET AL. 'Topical Diclofenac in the Treatment of Ocular Pain After Excimer Photorefractive Keratectomy' see abstract ---	1-24
X	SURV.OPHTHALMOL., vol.38, no.SUPP, July 1993 pages 141 - 148 Z.BALLAS ET AL. 'Clinical Evaluation of Ketorolac Tromethamine 0.5% Ophthalmic Solution for the Treatment of Seasonal Allergic Conjunctivitis' see page 145, Discussion --- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 1995	21.03.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Theuns, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	CLIN. TRIALS J., vol.21, no.2, 1984 pages 59 - 66 M.G.HECHANOVA, JR. 'A DOUBLE-BLIND STUDY COMPARING SODIUM CROMOGLYCATE EYE OINTMENT WITH PLACEBO IN THE TREATMENT OF CHRONIC ALLERGIC CONJUNCTIVITIS' see abstract	1-24
X	ANN. ALLERGY, vol.58, no.2, 1987 pages 109 - 112 M.L.RUGGIERI ET AL. 'Double-blind group comparative trial of sodium cromoglycate eye ointment and placebo in the treatment of allergic eye diseases' see page 110; table 2	1-24
X	JPN.J.OPHTHALMOL., vol.42, no.2, February 1988 pages 179 - 182 T.HIRAMITSU 'Topical aspirin solution relieved acute pain due to contact lens wear' see abstract	1-24
X	AM.J.OPHTHALMOL., vol.112, no.2, 15 August 1991 J.FRUCHT-PERY ET AL. 'The Effect of Topical Administration of Indomethacin on Symptoms in Corneal Scars and Edema' see the whole document	1-24
X	SURV.OPHTHALMOL., vol.38, no.SUPP, July 1993 pages 133 - 140 D.G.TINKELMAN 'Double-Masked, Paired-Comparison Clinical Study of Ketorolac Tromethamine 0.5% Ophthalmic Solution Compared with Placebo Eyedrops in the Treatment of Seasonal Allergic Conjunctivitis' see abstract	1-24
X	J. CATARACT REFRACT. SURG., vol.19, no.4, July 1993 pages 481 - 487 J.E.BLAYDES ET AL. 'Flurbiprofen 0.03% for the control of inflammation following cataract extraction by phacoemulsification' see page 485; table 4	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 95/00003

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 13-24 are directed to a method of treatment of the human/animal body the search has been based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.